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7-Valent pneumococcal conjugate vaccine and lower respiratory tract infections: Effectiveness of a 2-dose versus 3-dose primary series

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ABSTRACT

Background: Immunogenicity studies suggest antibody responses from a 7-valent pneumococcal conjugate vaccine (PCV7) regimen consisting of 2 doses in the primary series are less immunogenic, for at least several vaccine serotypes, compared with a regimen consisting of 3 doses; evidence of effectiveness for prevention of invasive pneumococcal disease for both regimens is available but comparative data are lacking for prevention of lower respiratory tract diseases (LRTD).
Methods: We compared rates of LRTD between children who were born in 2002 and received 2 versus 3 PCV7 doses in the primary series, both before and after receipt of the booster dose, using a retrospective matched-cohort design and health insurance claims data. Two-dose and 3-dose children were matched (1:1) using propensity scoring. Cumulative rates of hospital admissions and outpatient visits for LRTD were tallied during the post-primary/pre-booster period and the post-booster period (to age 3 years), respectively.
Results: During the post-primary/pre-booster period, 3-dose children ($n = 3293$) had 7.8 (95% CI: 0.8 to 14.8) fewer LRTD-related hospital admissions (per 1000 children) and 57 (95% CI: −6 to 128) fewer LRTD-related outpatient visits (per 1000 children) than matched 2-dose subjects ($n = 3293$). During the post-booster period, the numbers of LRTD-related hospital admissions and outpatient visits did not differ significantly between 3-dose and 2-dose children.
Conclusions: Our findings suggest that a 2-dose PCV7 primary series, while conferring savings from reduced vaccine costs in comparison with a 3-dose primary series, also may confer less protection against LRTD in the first year of life, at least during the period soon after the vaccine is introduced.

1. Background

Invasive pneumococcal disease (IPD) in children is a major cause of morbidity and mortality throughout the world despite the availability of effective antimicrobial therapy. Following nasopharyngeal colonization, bacteremia may result in disease of the central nervous system, pleural space, peri-orbital tissue, bone, or joints. Alternatively, contiguous spread from the nasopharynx to mucosal surfaces of the lung and middle ear may result in pneumonia or acute otitis media.

The universal immunization program for infants and toddlers in the US with 7-valent pneumococcal conjugate vaccine (PCV7) has resulted in a dramatic reduction of IPD due to each of the seven vaccine serotypes in children and adults [1–3]. Similar reductions in IPD due to vaccine serotypes in children have been reported in Canada, France, and Spain [4–6]. Lower respiratory tract disease (LRTD), the leading cause of death among children under 5 years of age, also declined following immunization with PCV7. A 26% decline in radiological proven pneumonia was observed in a large clinical trial conducted at Northern California Kaiser Permanente (NCKP) [7]. Bacteremic pneumonia due to vaccine serotypes (VST) declined by 70% in Gambia following immunization with PCV9, and overall pneumonia decreased 37% [8]. A post-marketing study in the US reported a 39% decline in all-cause hospitalized pneumonia in children less than 2 years of age [9]. These impressive results were achieved (largely) with 3-dose infant regimens, with and without booster doses.

Recently, several countries and provinces have introduced alternative regimens with 2 infant doses followed by a booster dose after 11 months of age [10,11]. Goldblatt and colleagues provided immunologic evidence that a reduced dosing regimen (with PCV9) might be equally protective [12]. They reported comparable serotype-specific IgG geometric mean concentrations at 5 months of age, prior to receipt of the booster dose, and during

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the 4-week period following receipt of the booster dose between infants receiving 2 doses at 2 and 4 months of age and those receiving 3 doses at 2, 3, and 4 months of age and successful priming for memory with both regimens. This finding contrasts with the diminished responses to 6B and 23F following a 2-dose primary series reported by Kayhty et al. [13]. Givon-Lavi and colleagues also reported decreased responses following a 2-dose primary series administered at 2 and 4 months of age compared with a 3-dose regimen (at 2, 4, and 6 months) for serotypes 6B and 23F [14].

In 2006, the Health Protection Agency in the UK recommended universal immunization with PCV7 using a 2-dose infant regimen (at 2 and 4 months) followed by a booster dose at 13 months, as well as a catch-up program thru age 23 months [15]. A dramatic decline in IPD cases due to the 7 serotypes has been reported in children aged <2 years in the UK [16]. Quebec introduced a universal infant immunization program with a 2-dose plus booster regimen (with 3 dose plus booster for high-risk children, and a catch-up program through age 5 years) beginning in December 2004, and reported a 70% decline in IPD and lobar pneumonia in children aged less than 5 years in 2006 [17]. Surveillance studies following the introduction of PCV7 in Norway also demonstrated a reduction in IPD following a 2-dose plus booster regimen [18,19]. Analysis of PCV clinical trial data with endpoints other than IPD suggests that a higher concentration of serum antibody may be necessary to prevent carriage, otitis media, and pneumonia [20,21]. As pneumonia is a major cause of morbidity and mortality globally, it is important to understand the impact of reduced dosing regimens on LRTD.

In 2002, only 18% of children had received 3 doses of PCV7 by 7 months of age and 39% by 19 months of age [22]. Shortages of PCV7 in the US during the first years following its introduction provide an opportunity to compare the frequency of respiratory tract disease before and after the booster dose between children who received reduced dosing regimens and those who received the recommended 3-dose primary series. We hypothesized that children who received only 2 infant doses in the primary series would experience more LRTD – prior to receipt of the booster dose – than infants who received a 3-dose infant regimen.

2. Methods

2.1. Data source

Data for this study were obtained from a large healthcare claims database (Medstat MarketScan Commercial Claims and Encounters Database), and spanned the period January 1, 2002 through December 31, 2005. The database is comprised of medical (i.e., facility and professional-service) and outpatient pharmacy claims from employer-sponsored health insurance plans covering 11 million persons in 2002, including employees as well as their spouses and dependents. The plans provide health benefits under a variety of products, including fee-for-service and capitated (full, partial) systems. Plan members reside throughout the US.

Data available for each facility and professional-service claim include the date and place of service, diagnoses (in International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM] format), procedures performed/services rendered (in Health Care Financing Administration Common Procedure Coding System [HCPCS], ICD-9-CM, and Uniform Bill-92 [UB-92] formats), discharge disposition (inpatient facility claims only), and quantity of services (professional-service claims only). Data available for each retail pharmacy claim include the drug dispensed (in National Drug Code [NDC] format), dispensing date, quantity dispensed, and number of days of therapy supplied. Selected demographic and eligibility information is also available for persons in the database, including age, sex, geographic location, coverage type, and the start and end dates of health insurance coverage. Patient-level data can be arrayed chronologically to provide a detailed longitudinal profile of all medical and pharmacy services used by each plan member.

All patient-identifying information has been either fully encrypted or removed from the database; it is therefore compliant with the Health Insurance Portability and Accountability Act of 1996 [23] and federal guidance on Public Welfare and the Protection of Human Subjects [24]. Per the Code of Federal Regulations, IRB review was not needed for a study of this nature, since "...subjects cannot be identified, directly or through identifiers linked to the subjects..." (45 CFR 46 §46.101).

2.2. Source population

The source population included all children in the database born between January 1, 2002 and December 31, 2002 who had comprehensive medical and drug benefits on their date of birth and received 2 or 3 PCV7 doses within their first 7 months of life (i.e., "primary series window"). Children with evidence of human immunodeficiency virus, immunodeficiency disorders, asplenia, or bone marrow or organ transplantation at anytime during the period of observation were excluded from the source population. A birth cohort from calendar year 2002 was specifically selected for analysis because PCV7 coverage levels in that year were limited due to shortages, thereby permitting an adequate number of 2-dose study subjects to be identified; potential confounding from indirect effects of vaccination were relatively low as the PCV7 had only been available and recommended beginning in June 2000.

2.3. Study population

Two separate – but not necessarily mutually exclusive – study populations were constituted from children identified in the source population. The first included matched pairs of children receiving 2 versus 3 PCV7 doses in the primary series, irrespective of subsequent receipt of the booster dose. This population was utilized in the comparison of post-primary/pre-booster disease burden. The second subpopulation consisted of matched pairs of children receiving 2 versus 3 PCV7 doses in the primary series, plus the PCV booster dose between ages 12 and 16 months ("booster window"), and was utilized to compare post-booster disease burden.

Children receiving 2 versus 3 PCV doses in each subpopulation were randomly matched – on a 1:1 basis, without replacement – based on closest estimated propensity score. Specifically, a logistic model was estimated – using data on all children in the source population – in which receipt of 2 versus 3 doses in the primary series (the dependent variable) was regressed on all characteristics (independent variables) hypothesized to be possibly related to the dependent variable, including birth month, age at receipt of booster (post-booster comparison only), sex, geographic region, health plan type, number of doses of other recommended childhood vaccines (including hepatitis B; diphtheria, tetanus, and pertussis; *Haemophilus influenzae* type b; inactivated polio), numbers of well-baby and illness-related visits, and the presence of selected high-risk conditions (including cardiac disease, chronic pulmonary disease, chronic kidney disease, diabetes, sickle cell anemia or other hemoglobinopathy, cerebrospinal fluid leak, and cochlear implant). Then, for each child in the source population, the predicted probability of receiving 2 versus 3 doses in the primary series (i.e., propensity score) was estimated based on the coefficients from the logistic regression model and corresponding characteristics of the child. Children in the 2-dose group were subsequently matched to children in the 3-dose group based on closest propensity score, within 0.01 (on a scale of zero to one).